

### REMARKS

Reconsideration and allowance are respectfully requested.

Claims 10 and 25-40 are pending. Non-elected claims 1-9 and 11-24 were withdrawn from consideration by the Examiner. Applicants have canceled the non-elected claims without prejudice to future prosecution of that subject matter.

New claims 25-26 are described on page 7, lines 21-23, and page 11, lines 1-4, of the specification. New claims 27-29 are described on page 7, lines 10-29, of the specification. New claim 30 is described on page 9, lines 10-12, of the specification. New claims 31-33 are described on page 10, lines 7-10, of the specification. New claims 34-35 are described on page 10, lines 16-20, of the specification. New claim 36 is described on page 9, lines 12-14, of the specification. New claim 37 is described on page 11, lines 22-25, of the specification. New claim 38 is described on page 12, lines 3-4, of the specification; new claim 39 is described on page 12, line 20, of the specification. New claim 40 is described by the page 11, lines 1-10, of the specification.

As seen from the foregoing, the amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

A signed copy of the Information Disclosure Statement filed August 2, 2000 is submitted herewith to hasten prosecution. It should be noted, however, that the cover sheet filed with the Information Disclosure Statement stated that "the signature below serves as the signature to the attachment in the absence of any other signature thereon." Therefore, the originally submitted paper was proper.

The hyperlink on page 9 of the specification has been deleted. Claim 10 has been amended to address the objection to use of acronyms. In view of the preceding, Applicants request withdrawal of the objections to the specification and claims.

### *35 U.S.C. 101 –Utility*

Only after the Patent Office provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the appli-

cant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Claim 10 was rejected under Section 101 because the invention allegedly "is not supported by either a substantial asserted utility or a well established utility." Applicants traverse because the specification's teaching that human pregnane X receptor (hPXR) can be used in a method of screening a test compound establishes a practical utility for the invention.

As seen from its name, hPXR is a member of the steroid hormone receptor family. The Office Action on pages 4-5 makes conclusions based on the incorrect assumption that Applicants have not taught ligands of hPXR. But as seen in Example 3 of the specification, many hPXR ligands are taught (e.g., dexamethasone-t-butylacetate, rifampicin, and clotrimazole). The data "indicate that structurally-divergent compounds can serve as hPXR ligands" (page 32, line 20-22, of the specification).

The allegation in the Office Action on pages 4-5 that Kliever et al. (1998) "teach that PXR ligand is not known" is contradicted by the later statement that Kliever et al. (1998) teach a binding assay with PXR and binding to pregnenolone steroids" on page 9. Thus, the Patent Office has not sustained its burden of showing that one of ordinary skill in the art would reasonably doubt the asserted utility because the allegation on which such a conclusion would be based on an incorrect assumption.

Withdrawal of the Section 101 rejection is requested because Applicants have taught that the claimed invention has patentable utility.

#### 35 U.S.C. 112 – Definiteness

Claim 10 was rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claim 10 has been amended to identify hPXR by its amino acid sequence. The method uses a protein comprised of a ligand binding domain of hPXR.

Applicants teach that hPXR can activate transcription of the CYP3A4. The metes and bounds of this limitation are clear: the CYP3A4 gene is expressed by transcription. The claim does not mention direct repeat response elements. Therefore, all that is

required by the claim is the screening of a test compound by its ability to bind a ligand binding domain of hPXR, and to determine that it induces CYP3A4 gene expression.

Finally, step iii) has been added to recite the result previously mentioned in the preamble.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

### *35 U.S.C. 112 – Enablement*

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claim 10 was rejected under Section 112, first paragraph, because the specification allegedly does not teach how to use the variants of the hPXR receptor. Applicants traverse because the modular structure of steroid hormone receptors is a well-known and art-accepted property.

Using this property, many changes are possible and it is even possible to switch ligand binding and DNA binding domains between steroid hormone receptors, or even DNA binding domains from other transcription factors or unrelated proteins (page 10, lines 16-28, of the specification). Example 6 teaches a biotin-His6-PXR/RXR $\alpha$  chimeric receptor that is functional.

As explained above, ligands for hPXR are known and Kliewer et al. (1998) does not support the conclusions asserted in the Office Action. A person of skill in the art would understand that substitutions, deletions, and additions can be made and used in the claimed invention without undue experimentation. By retaining the ligand binding domain of hPXR, the ligand specificity of variants should also be retained. Whether or not hPXR binds ligand is a matter of routine experimentation. For example, Kliewer et al. (1998) shows cortisol and corticosterone are not ligands.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

*35 U.S.C. 102 – Novelty*

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 10 was rejected under Section 102(b) as allegedly being anticipated by Kliewer et al. (Cell, 1998). Applicants traverse because the cited reference presents their work as the disclosure therein applies to the invention, and is not the work of another. Applicants made the invention before the cited reference was printed.

Claim 10 was rejected under Section 102(b) as allegedly being anticipated by Evans et al. (WO 96/22390). Applicants traverse because all claim limitations are not found in the cited reference. Evans et al. discloses an orphan nuclear receptor XOR-6, which is different from hPXR. The claimed invention requires hPXR.


Withdrawal of the Section 102 rejections is requested.

Having fully responded to all of the pending objection and rejections of the Office Action (Paper No. 16), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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**APPENDIX**

**MARKED-UP VERSION TO SHOW CHANGES**

**IN THE SPECIFICATION**

The specification is amended as follows.

Pages 8-9, second paragraph starting on page 8, line 10:

One embodiment of the receptor of the invention has the amino acid sequence set forth in Figure 1, or an analog thereof (wherein the term analog is intended to indicate a naturally occurring human variant of the Figure 1 sequence), or a fragment thereof, including fragments having at least one functional characteristic of hPXR (e.g., ligand binding or DNA binding). Preferred fragments include portions of the Figure 1 sequence at least 30 consecutive amino acids in length, more preferably, at least 50 consecutive amino acids in length, and most preferably, at least 75 consecutive amino acids in length. Specific fragments include the ligand binding domain (that is, amino acids 141 to 434 of the Figure 1 sequence) and the DNA binding domain (that is, amino acids 41 to 107 of the Figure 1 sequence) as well as the domain that is used for the ligand binding assay described in the Examples that follow (that is, amino acids 130-434 of the Figure 1 sequence). The invention also includes a protein comprising a domain sharing at least 80% amino acid sequence identity with the ligand binding domain of the Figure 1 sequence, more preferably, at least 85% amino acid sequence identity and, most preferably, at least 90% or 95%, 96%, 97%, 98% or 99% amino acid sequence identity with the ligand binding domain of the Figure 1 sequence (% sequence identity being determined, for example, by Basic Blast (version 2.0) available through the NCBI website [<http://www.ncbi.nlm.nih.gov/>]), and, advantageously, retaining the function of the Figure 1 sequence.

**IN THE CLAIMS**

The claims are amended as follows.

10. (Amended) A method of screening a test compound for its ability to induce cytochrome P-450 3A4 (CYP3A4) gene expression comprising

i) contacting said test compound with a protein comprised of a [the] ligand binding domain of human pregnane X receptor (hPXR) having the amino acid sequence of SEQ ID NO:14,

ii) determining whether said test compound binds to said protein [ligand binding domain], and

iii) determining whether a test compound that binds to said protein induces CYP3A4 gene expression

[wherein binding of the test compound to said ligand binding domain is indicative of a compound that induces CYP3A4 gene expression].

Claims 1-9 and 11-24 are canceled without prejudice or disclaimer.

Claims 25-40 are added as new claims.